Klinik und Poliklinik für Innere Medizin
Direktor: Prof. Dr. med. E. Battegay

Arbeit unter Leitung von Prof. Dr. med. M. Scharl

The use of biologicals in the treatment of inflammatory diseases: a single center experience in a large Swiss university hospital

INAUGURAL-DISSERTATION
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vorgelegt von
Salomon Miro Manz

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Contents

Abstract

Background: Current therapy for inflammatory diseases is glucocorticoids (GCs) either as monotherapy or combined with immunosuppressive medications. The side effects of the GCs are often limiting, therefore new therapeutic options are urgently required. Biological agents such as rituximab, tocilizumab or anti TNF antibodies showed promising results. Hence, we investigated the impact of biologicals on the prescription of GCs, clinical improvement and laboratory findings.

Method: We performed a retrospective analysis of the medical history of 44 cases of severe or relapsing inflammatory diseases, which were not appropriately controlled with standard immunosuppressive therapy. Our focus was on GCs dosage, clinical improvement and inflammatory parameters.

Results: Rituximab treatment (*n* = 18) resulted in a significant decrease in the daily prednisone dosage and also a clear decrease in CRP levels and leucocyte counts. Another group of 10 patients were treated with anti TNF antibodies (adalimumab *n* = 8, infliximab *n* = 1, etanercept *n* = 1) and displayed an obvious decrease in the daily prednisone dosage as well as a significant decrease of the CRP level. Treatment of patients (*n* = 5) with tocilizumab showed a pronounced reduction of the daily prednisone dosage, whereas the decrease in CRP levels as well as leucocyte counts was less distinct. Patients treated with anti interleukin 1 antibodies (anakinra *n* = 10, canakinumab *n* = 1) showed also a pronounced decrease of the daily prednisone dosage, whereas again the reduction of CRP levels and the leucocyte counts was less distinct. Furthermore, 34 of 39 patients (87%, 5 no data) had a clinical improvement of their symptoms after 24 weeks of treatment.

Conclusion: We demonstrate that the GCs dosage can be reduced and the laboratory inflammation parameters tend to normalization under the treatment with biological agents. Biologicals should be considered if a patient with severe or relapsing inflammatory diseases cannot be treated with the standard immunosuppressive therapy or exerts severe side effects.

1. Introduction

Systemic vasculitides represent a heterogeneous group of inflammatory diseases commonly affecting the arterial and/or venous blood vessels. Characteristic for the vasculitis manifestations are on the on hand generalized symptoms such as weight loss or fever, but on the other hand also specific symptoms that strictly depend on the localization of the affected blood vessels. Due to the chronic inflammation an injury or occlusion the affected blood vessels can occur, which leads to a hypoperfusion and finally damage of the affected organ system. Crucial for the correct diagnosis is the particular patient history as well as the clinical findings. A biopsy of the suspicious lesion, radiological methods such as angiography or duplex-ultrasound, and blood analysis, e.g. for specific autoantibodies, are often needed to confirm the diagnosis (1). An annual incidence of 40 to 54 cases per one million persons is reported (2) and it seems that the incidence depends on age, season and location (3).

According to the latest Chapel-Hill classification from 2012 it has to be distinguished between small vessel vasculitis, medium vessel vasculitis and large vessel vasculitis. A further group is represented by secondary vasculitis, such as rheumatoid vasculitis, drug-induced vasculitis or virus infection associated with vasculitis (HBV, HCV or HIV) (4) (5). Without treatment, vasculitis can become a life-threatening condition exerting disabling disease manifestations. An induction treatment followed by a long-term maintenance therapy is needed to control the disease.

Systemic autoimmune disorders represent a heterogeneous group of inflammatory diseases which can affect multiple organ systems (e.g. Systemic Lupus Erythematosus (SLE), Sjögren's syndrome, etc.). General symptoms such as fever, fatigue, weight loss or night sweats and specific symptoms depending on the effected organ system are typical. Determining for the correct diagnosis are the patient history, clinical findings and blood analysis (e.g. for specific autoantibodies).

The prevalence of SLE is 50 per 100’000 and mostly women are affected (90% of the patients) (6). Increased inflammatory disease activity and progressive organ damage result in substantial morbidity and mortality (6, 7). Disease flares may occur even with what seems to be the ideal treatment at the moment (8).

Autoinflammatory diseases encompass a group of disorders characterized by recurrent episodes of inflammation without a known trigger (e.g. TRAPS). They share a genetic background and are caused by mutations in genes coding proteins directly involved in the biology of inflammasome, in which interleukin 1 (IL-1), a proinflammatory cytokine and important mediator of the systemic inflammatory

response, plays a crucial role. In contrast to autoimmune diseases, no high titer autoantibodies or specific-T or B-cell autoreactivity are detected.

To date, the most common therapy for inflammatory diseases are glucocorticoids (GCs) either as monotherapy or combined with certain immunosuppressive medications such as cyclophosphamide (CYC), azathioprine (AZA) or methotrexate (MTX) (3). However, therapy failure and disease relapses are common (9, 10) (37). An additional limitation of this treatment is the cumulative toxicity and side effects of immunosuppressants like CYC or MTX (11). Another limitation of the treatment are the various side effects of the GCs such as gain of weight, Cushing's syndrome, arterial hypertension, gastrointestinal bleeding, gastrointestinal ulcers, depression, cataract, osteoporosis, diabetes mellitus, opportunistic infections and a risk factor for thromboembolism (12-20). The side effects depend on different factors like the duration of the treatment, dosage, daytime of the administration and the application form. Due to the described side effects it is a major goal in treatment to reduce to GCs dosage as fast and as much as possible.

Based on the above described problems with current therapy approaches, it is obviously of great interest on the one hand to obtain an additional treatment option for patients with therapy failure and/or disease relapses as well as to reduce the needed GCs dosage to maintain remission. In the last few years so-called biologicals (e.g. rituximab (RTX): anti CD20 antibody, tocilizumab (TCZ): anti interleukin 6 receptor antibody, infliximab (IFX)/adalimumab (ADA): anti TNF antibodies) were tested for the use in patients featuring a severe clinical disease course (3).

Previous case series and observational studies have demonstrated an effect of biological treatment in inflammatory diseases. Nevertheless, large RCTs are required to clarify to role of biological agents in the treatment of vasculitis (3).

However, also these new biologicals can exert severe side effects and some special examinations are required before their use. For RTX it is necessary to screen the patients for hepatitis B, because it can exacerbate or reactivate the infection. For IFX/ADA it is important to screen for latent tuberculosis, because TNF inhibitors can reactivate tuberculosis, and also for viral hepatitis. Rare cases of a perforated diverticulitis under the treatment with TCZ where reported. Hence, status post diverticulitis or intestinal perforation seems to be a relative contraindication.

All in all, data about the use of these novel therapeutic agents in patients with inflammatory diseases are promising, but nevertheless rare and still unanswered questions about the effectiveness and safety of the biological agents

remain. Therefore, our study aims to analyze the impact of a treatment with biological agents on the clinical course, a possible reduction of the dosage of GCs as well as safety issues in patients suffering from inflammatory diseases.

2. Method

We retrospectively analyzed 44 cases of patients receiving biologic agents as off-label treatment for inflammatory diseases at the Division of Internal Medicine, University Hospital Zurich, Switzerland between 2006 and 2014. The biologicals used were: rituximab (anti CD20 antibody), adalimumab (anti TNF antibody), infliximab (anti TNF antibody), etanercept (anti TNF antibody), tocilizumab (anti interleukin 6 receptor antibody), anakinra (anti interleukin 1 receptor antibody) and canakinumab (anti interleukin 1beta antibody).

A detailed review of each patient's medical record was undertaken, focusing on the medical treatment (before and concurrent to the biological treatment), secondary diagnoses, blood chemistry and hematology values, the concurrent medication and disease outcome during and/or after treatment. The data was collected on the first biological agent administration, six weeks and 24 weeks later.

The statistical analysis was performed using ANOVA (One-way Analysis of Variance) in the program GraphPad InStat. The figures were created with KaleidaGraph.

3. Case Presentation and Results

3.1 Anti CD20 Antibody: Rituximab (RTX)

18 patients (mean age 50 years, 6 male, 12 female) were treated with rituximab. Thereof, seven patients had granulomatosis with polyangiitis (GPA), one eosinophilic granulomatosis with polyangiitis, four SLE, three Sjögren's syndrome, one microscopic polyangiitis, one myasthenia gravis and one suspected ORL manifestation of an IgG4 related disease. For further information please refer to table 1 (Appendix).

As induction therapy in patients with vasculitis, RTX is given 1000 mg two infusions of 1000 mg each two weeks apart or 375 mg/m^2/week for four weeks (21). For maintenance of remission, RTX should then be administered every six month in a dosage of 500 mg (22, 23). All of our patients were treated according to this scheme.

In patients with RTX treatment the baseline prednisone dosage at RTX treatment start was 29.3 mg/d. After a period of six weeks, the mean prednisone dose decreased to 20.6 mg/d and a further reduction down to 6.8 mg/d was noted after 24 weeks of RTX treatment (figure 1a). Figure 1b shows the individual prednisone dosage reduction during the 24 weeks of RTX treatment. A downward trend of the prednisone dosage was noticeable, although one patient needed an increased dosage after six weeks. The numbers of the patients refer to table 1 (Appendix).

At the beginning of the RTX treatment the baseline CRP was 9.7 mg/l. Within the first six weeks of treatment there was a reduction to 5.1 mg/l and after 24 weeks in total it decreased to 3.7 mg/l as shown in figure 1c. Fig. 1d depicts for each patient the course of CRP, whereas a general downward trend can be observed.

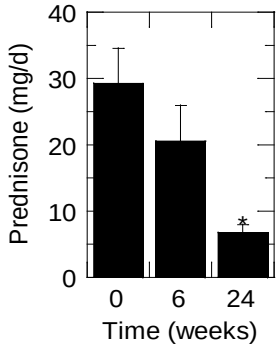

*Fig. 1a: Mean prednisone dosage reduction during treatment with rituximab (*p < 0.0016 vs. week 0).*

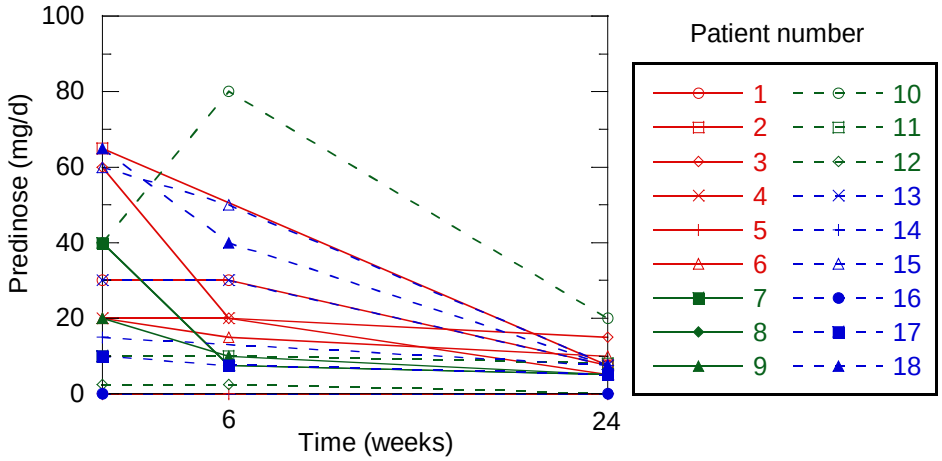

Fig. 1b: Individual prednisone dosage reduction during treatment with rituximab (patient numbers refer to Tab. 1).

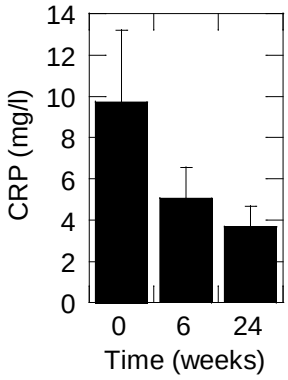

Fig. 1c: Mean CRP concentration reduction during treatment with rituximab.

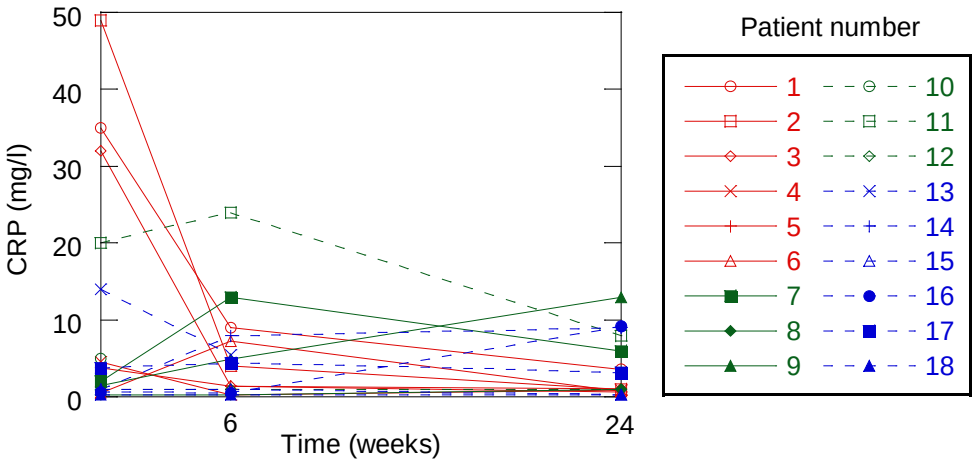

Fig. 1d: Individual CRP concentration reduction during treatment with rituximab (patient numbers refer to Tab. 1).

The mean baseline of leucocytes count was 8.2 G/l at RTX treatment start. It decreased to 8.0 G/l after six weeks of treatment. A further reduction to 7.1 G/l was noted after 24 weeks of treatment with RTX (figure 1e). Figure 1f shows the leucocytes count as a function of time for each patient.

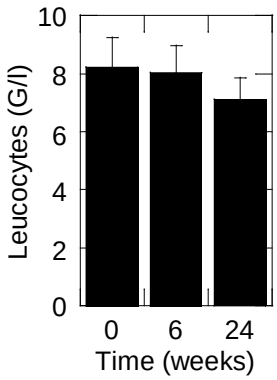

Fig. 1e: Mean leucocytes count during treatment with rituximab.

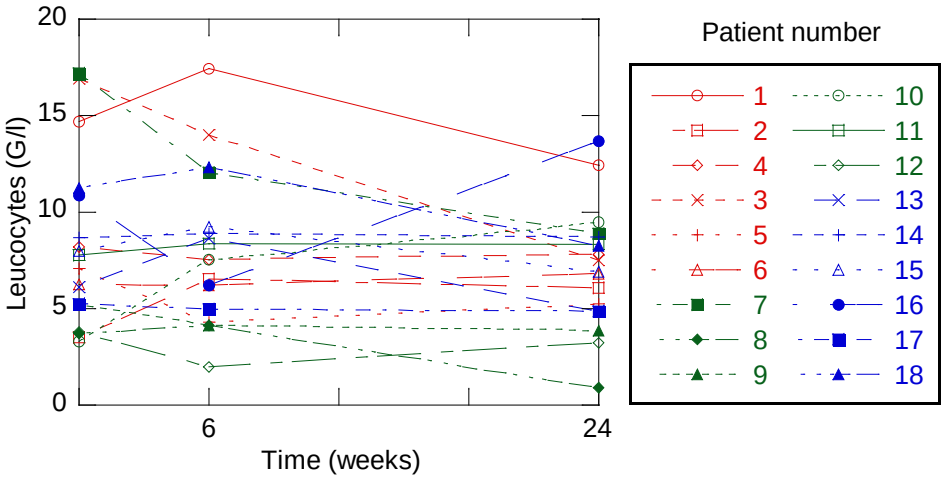

Fig. 1f: Individual leucocytes count during treatment with rituximab (patient numbers refer to Tab. 1).

The secondary diagnoses are listed in figure 2. It is noticeable that diseases of the metabolic syndrome e.g. arterial hypertension, diabetes mellitus, obesity and hyperuricemia and other side effects of the GCs such as depression, osteopenia or s.p. venous thromboembolism are very common.

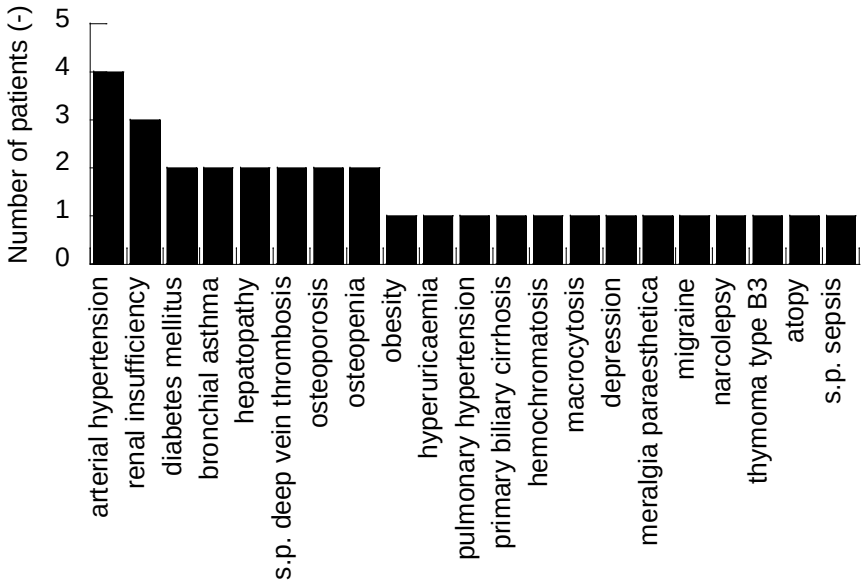

Fig. 2: Secondary diagnoses of the patients treated with rituximab.

3.2 Anti TNF Antibodies: Adalimumab (ADA), Infliximab (IFX), Etanercept (ETN)

10 patients (mean age 45, 4 male, 6 female) were treated with either one of three different anti TNF antibodies or TNF inhibitors, respectively (adalimumab *n* = 8, infliximab *n* = 1, etanecerpt *n* = 1). In this group, two patients suffered from Behcet's disease, two Takayasu's arteriitis, one undifferentiated small vessel vasculitis, one Henoch-Schoenlein purpura, one polyarteriitis nodosa, one ulcerative leukocytoclastic vasculitis, one recurrent polychondritis and one tumor necrosis receptor-associated periodic syndrome (TRAPS). For further information please refer to table 2 (Appendix).

ADA was given 40 mg every two weeks. The normal dosage of IFX is 5 mg/kg body weight in week zero, two and six as an induction therapy and then every six weeks as a maintenance therapy. The patient who was treated with ETN received 25 mg twice a week.

In patients with ADA treatment the baseline prednisone dosage was 35.9 mg/d at the treatment beginning. Six weeks later there was a reduction down to 23.4 mg/d and after 24 weeks of ADA treatment a further decrease to 9.7 mg/d (fig. 3a). Figure 3b shows the individual prednisone dosage during the 24 weeks of ADA treatment. A downward trend of the prednisone dosage was observable, although one patient needed an increased dosage after six weeks and another patient received an increased dosage after 24 weeks. The numbers of the patients refer to table 2 (Appendix).

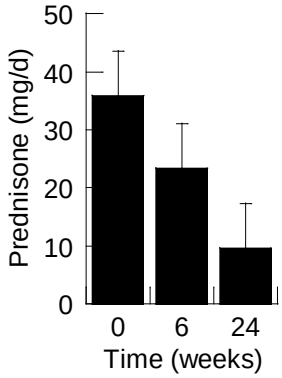

Fig. 3a: Mean prednisone dosage during treatment with adalimumab.

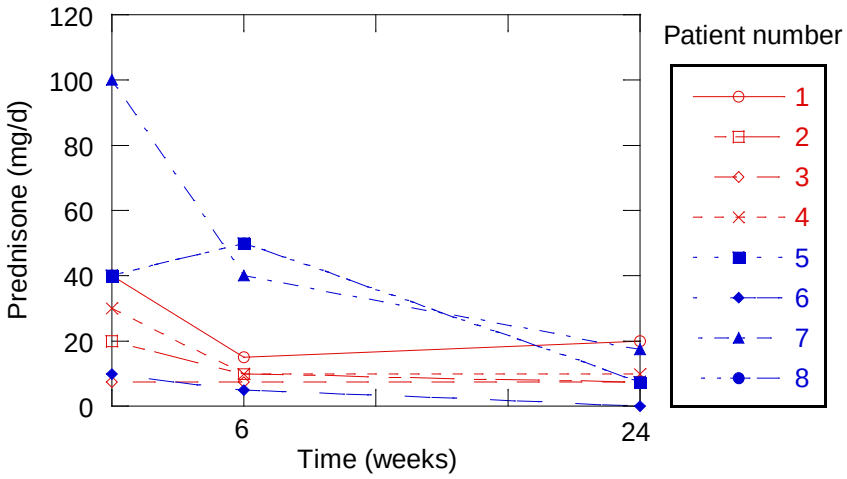

Fig. 3b: Individual prednisone dosage reduction during treatment with adalimumab (patient numbers refer to Tab. 2).

The CRP baseline at ADA treatment start was 23.3 mg/l. There was a significant reduction (0 vs 6 weeks, $p<0.05$) down to 4.1 mg/l after six weeks and a further decrease to 2.0 mg/l after 24 weeks (0 vs 24 weeks, $p<0.05$) with ADA treatment (figure 3c). The individual CRP level is shown in figure 3d. After 24 weeks of ADA treatment all patients had a maximum CRP of 5 mg/l.

At treatment start with ADA the baseline of the leucocytes count was 8.8 G/l. It increased to 9.1 G/l after six weeks but after 24 weeks of ADA treatment the leucocytes count decreased to 8.4 G/l as shown in figure 3e. While some patients displayed a decrease of the leucocytes count, others showed an increase (Figure 3f).

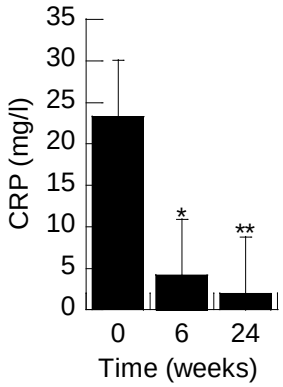

Fig. 3c: Mean CRP concentration during treatment with adalimumab (p < 0.05 vs. week 0, ** p < 0.05 vs. week 0).*

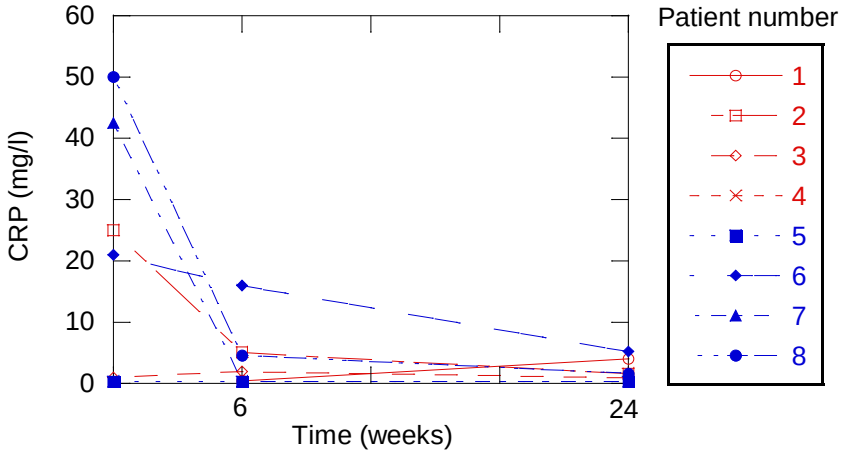

Fig. 3d: Individual CRP concentration reduction during treatment with adalimumab (patient numbers refer to Tab. 2).

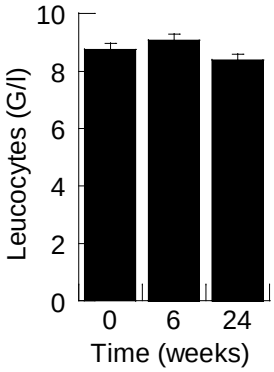

Fig. 3e: Mean leucocytes count during treatment with adalimumab.

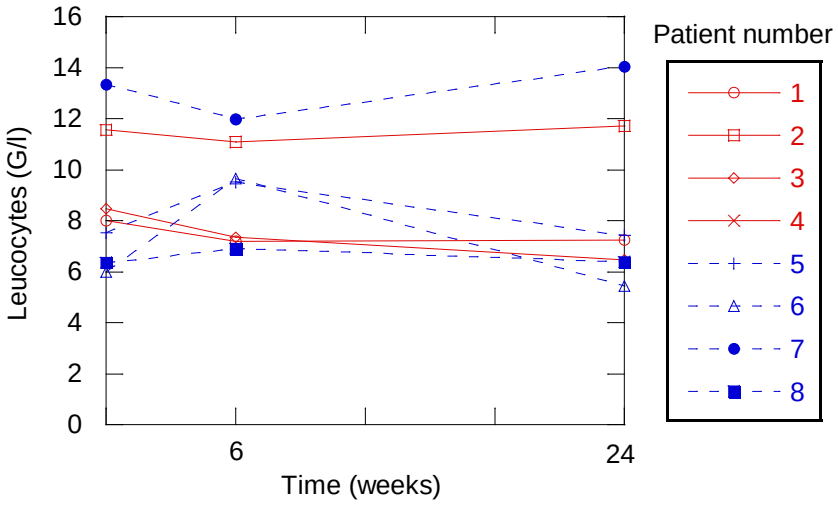

Fig. 3f: Individual leucocytes count during treatment with adalimumab (patient numbers refer to Tab. 2).

Only one patient was treated with IFX and one with ETN within the investigated time period. The GCs dosage of the patient who received IFX was still at 20 mg/d after six weeks. The patient died before the next follow up.

The patient who was treated with ETN received prednisone 60 mg/d in week zero and was then lost to follow up.

The secondary diagnoses are listed in figure 4. It is again noticeable that diseases of the metabolic syndrome such as diabetes mellitus and obesity and the other side effects of the GCs treatment (e.g. depression, osteoporosis, venous thromboembolism) are common.

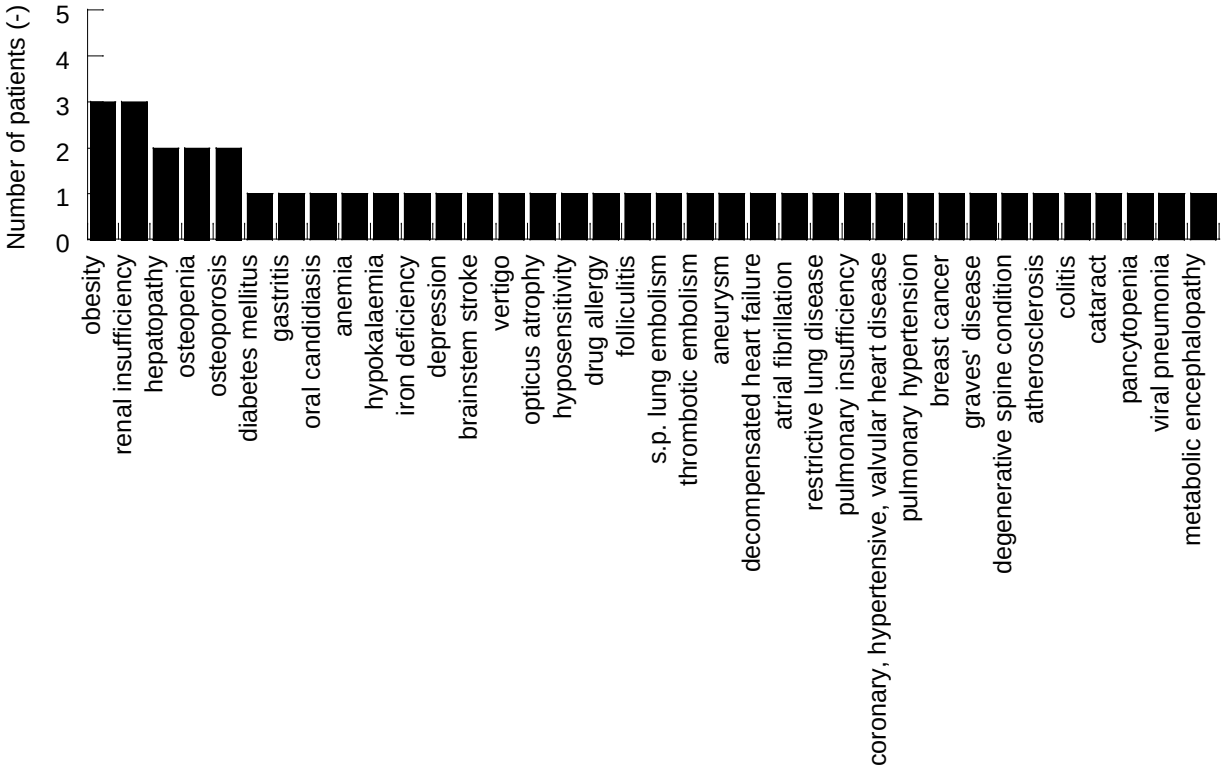

Fig. 4: Secondary diagnoses of the patients treated with anti TNF antibodies.

3.3 Anti Interleukin 6 Receptor Antibody: Tocilizumab (TCZ)

Five patients (mean age 58, 1 male, 4 female) received tocilizumab. Thereof, two patients suffered from temporal arteriitis, one from large vessel vasculitis, one from Takayasu's arteritis and one from Castleman's disease.

The dosage of TCZ was 8 mg/kg body weight every four weeks. In patients treated with TCZ the baseline prednisone dosage was 11.5 mg/d at treatment beginning. A reduction to 7.5 mg/d six weeks later and a further decrease down to 4.9 mg/d was observable after 24 weeks (figure 5a). The individual prednisone dosage is shown in figure 5b. The downward trend was noticeable, even though one patient needed an increased dose after six and 24 weeks. The numbers of the patients refer to table 3 (Appendix).

At the beginning of TCZ treatment the baseline CRP was 6.9 mg/l and it decreased to 4.6 mg/l after six weeks. A slight increase up to 5.8 mg/l was observed after 24 weeks (figure 5c). Figure 5d shows the individual CRP levels. A downward trend of the CRP occurred, although one patient had an elevated CRP after six weeks and another patient after 24 weeks.

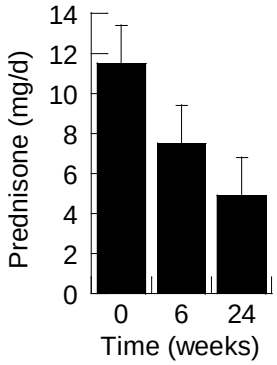

Fig. 5a: Mean prednisone dosage during treatment with tocilizumab.

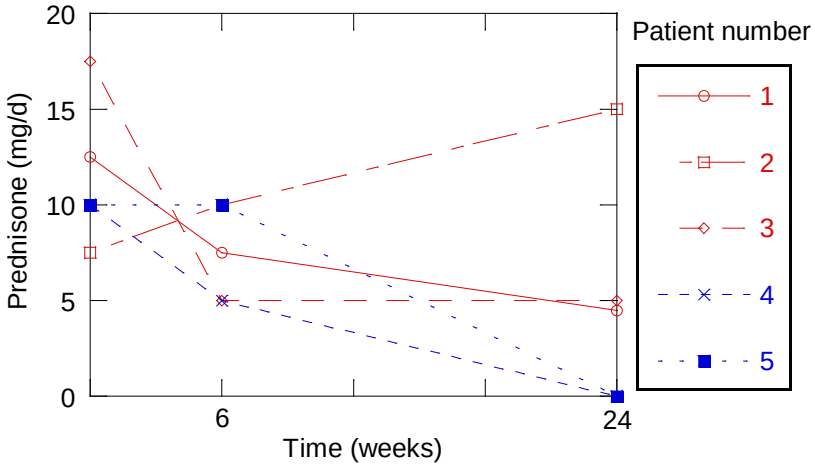

Fig. 5b: Individual prednisone dosage during treatment with tocilizumab (patient numbers refer to Tab. 3).

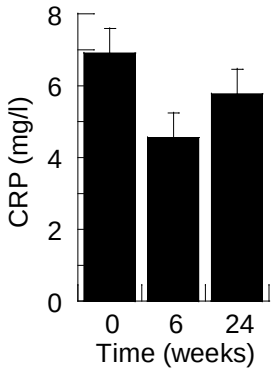

Fig. 5c: Mean CRP concentration during treatment with tocilizumab.

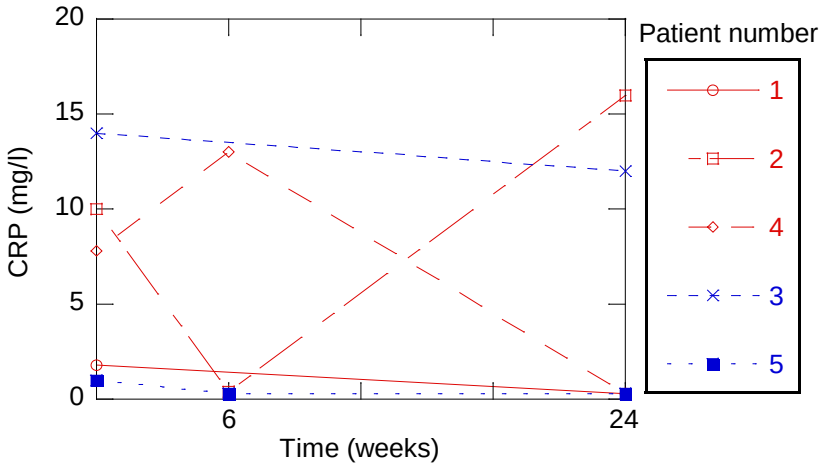

Fig. 5d: Individual CRP concentration during treatment with tocilizumab (patient numbers refer to Tab. 3).

The baseline of leucocytes count was 10.8 G/l at TCZ treatment start. There was a reduction down to 8.0 G/l after six weeks and a further reduction to 7.9 G/l after 24 weeks was observable (figure 5e). The individual leucocytes count is shown in figure 5f. A downward trend of the leucocytes count occurred even though two patients had an increased leucocytes count after 24 weeks.

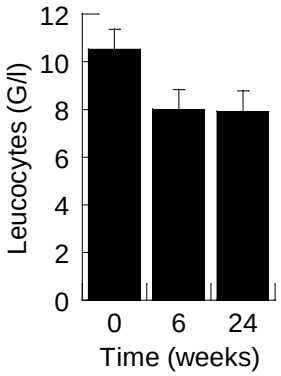

Fig. 5e: Mean leucocytes count during treatment with tocilizumab.

The secondary diagnoses are listed in figure 6. The side effects of the GCs such as osteopenia, osteoporosis and diabetes mellitus or arterial hypertension were observed.

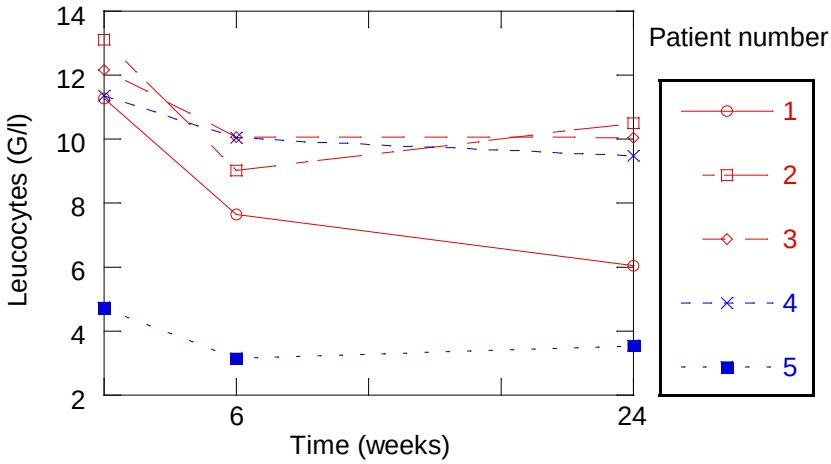

Fig. 5f: Individual leucocytes count reduction during treatment with tocilizumab (patient numbers refer to Tab. 3).

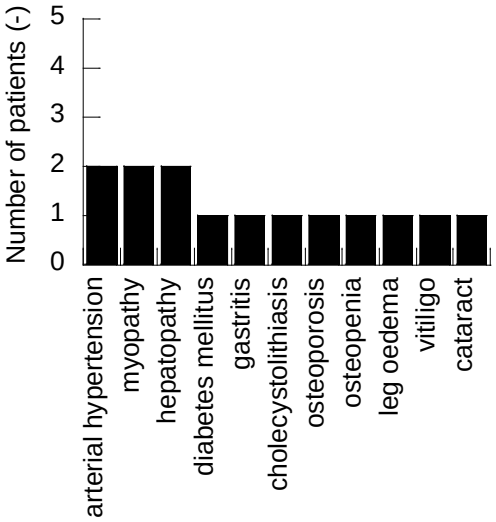

Fig. 6: Secondary diagnoses of the patients treated with tocilizumab.

3.4 Interleukin 1 Blockade: Anakinra (ANK) and Canakinumab (CKN)

11 patients (mean age 38, 1 male, 10 female) were treated with interleukin 1 blockade (anakinra *n* = 10, canakinumab *n* = 1). Thereof, four patients had juvenile idiopathic arthritis, two periodic fevers with aphthous stomatitis, pharyngitis, and adenitis (PFAPA) syndrome, two chronic systemic inflammation, one Behcet's disease, one neutrophilic dermatosis and one tumor necrosis receptor-associated periodic syndrome (TRAPS). For further information please refer to table 3 (Appendix).

At the beginning of ANK treatment the baseline prednisone dosage was 16.3 mg/d. After six weeks a reduction to 4.0 mg/d and a further reduction down to 3.4 mg/d after 24 weeks was observable (figure 7a). The individual prednisone dosage is shown in figure 7b. A downward trend of the prednisone dosage was visible, although one patient needed an increased dosage after 24 weeks. The numbers of the patients refer to table 3 (Appendix).

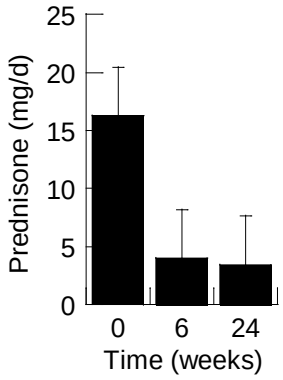

Fig. 7a: Mean prednisone dosage during treatment with anakinra.

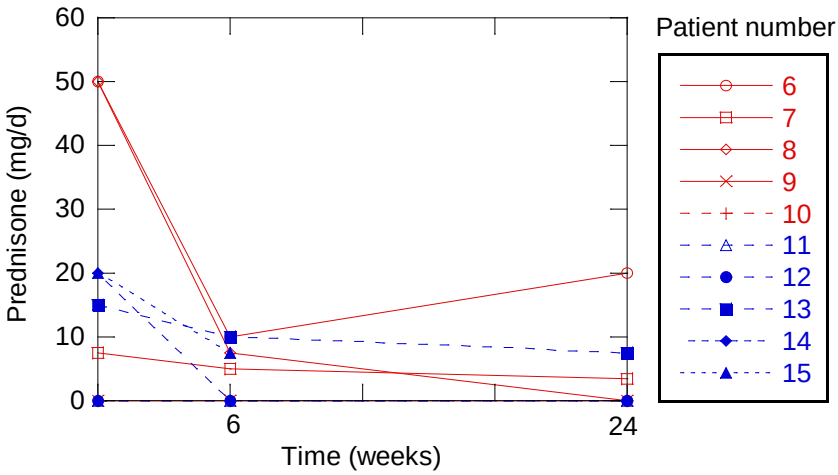

Fig. 7b: Individual prednisone dosage during treatment with anakinra (patient numbers refer to Tab. 3).

The baseline CRP at treatment start with ANK was 25.7 mg/l. There was a reduction to 11.4 mg/l after six weeks, but after 24 weeks it increased to 15.5 mg/d (figure 7c). Figure 7d shows the individual CRP. While most of the patients exhibited a reduction of the CRP, others displayed a slight increase after six weeks and one patient had a pronounced increase.

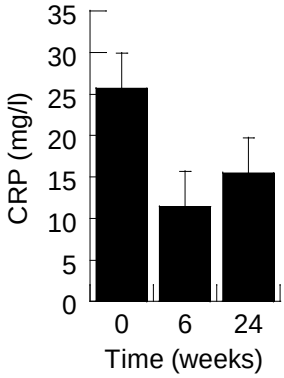

Fig. 7c: Mean CRP concentration during treatment with anakinra.

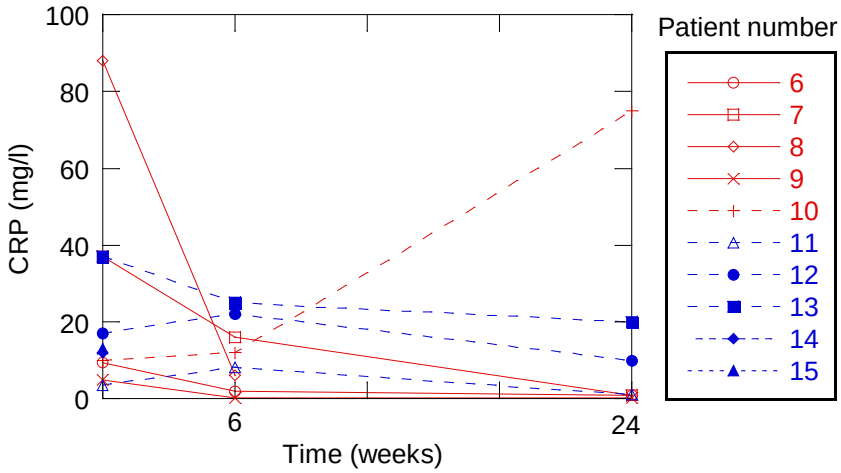

Fig. 7d: Individual CRP concentration reduction during treatment with anakinra (patient numbers refer to Tab. 3).

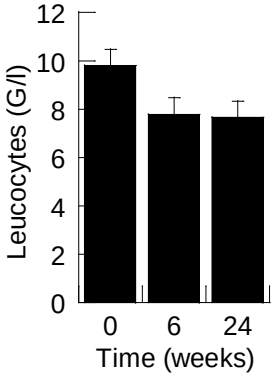

Fig. 7e: Mean leucocytes count during treatment with anakinra.

The baseline of the leucocytes count at ANK treatment start was 9.8 G/l. A decrease to 7.8 G/l after six weeks and a further reduction down to 7.7 G/l after 24 weeks was found (figure 7e). The individual leucocytes count is shown in figure 7f, where some patients displayed a decrease others an increase.

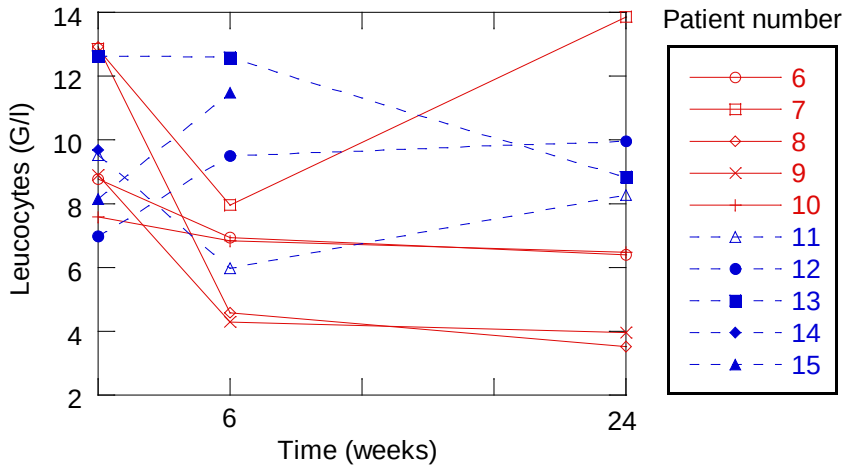

Fig. 7f: Individual leucocytes count reduction during treatment with anakinra (patient numbers refer to Tab. 3).

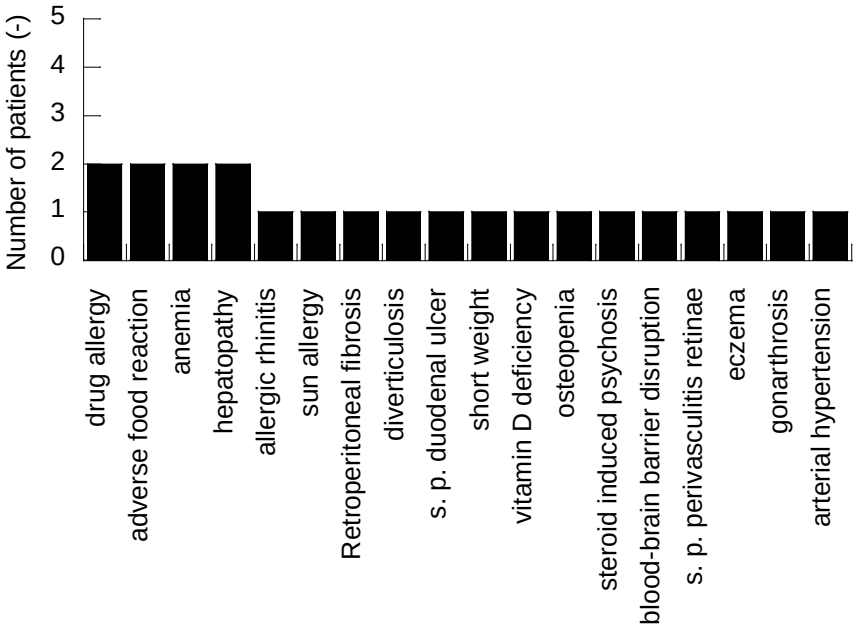

Fig. 8: Secondary diagnoses of the patients treated with anakinra and canakinumab.

One patient with TRAPS was treated with CKN. At treatment start he received prednisone 20 mg/d but no blood chemistry or hematology analysis was done. No information about the medication after six and 24 weeks was available. Six weeks later the leucocytes count was 6.6 G/l and the CRP was 2.8 mg/l. The leucocytes count increased to 8.4 G/l after 24 weeks. No information about the CRP was recorded.

The secondary diagnoses are listed in figure 8.

4. Discussion

This study demonstrates that biological agents combined with GCs reduce the daily GCs dosage necessary to control inflammation and vasculitis symptoms and, therefore, finally reduce GC related side effects. This is supported by the fact that the laboratory findings of the inflammation parameters for most of the patients trend towards normalization.

The necessary daily prednisone dosage is significantly reduced under RTX treatment after 24 weeks. Furthermore the mean CRP level is reduced to a physiological level. It seems likely that the decrease of the leucocytes count is due to the reduction of the daily GCs dosage as well as the declining inflammation, which is caused by the biological agents. All seven patients with GPA achieved remission after 24 weeks of treatment with RTX. Similar results were found by Cartin-Ceba et al. (2012) (24). Two out of four patients with SLE had a clinical improvement after 24 weeks. Diaz-Lagares et al. (2011) described a therapeutic response of the renal function in 67% of the patients (25). Two out of three patients with Sjögren's syndrome showed a clinical improvement after 24 weeks. The third patient was lost to follow up. A significant improvement of fatigue and global health was shown by Dass et al (2008) (26). However, a multicenter RCT from 2014 could not verify those findings (27). In general, RTX was well tolerated, and no serious adverse effect was observable during treatment. Similar results were found by Cartin-Ceba et al. (2012)(24).

In this study the daily GCs dosage was reduced after six and 24 weeks of treatment with ADA. In addition, the CRP level significantly decreased after six and 24 weeks ($p<0.05$). The leucocytes count was in the physiological range during the study. One of two patients with Behcet's disease showed a clinical improvement after 24 weeks. Perra et al. (2012) (28) described a complete or partial improvement in 17 of 19 patients with Behcet's disease (89%). Two patients with Takayasu's arteriitis were treated with ADA and both showed a clinical improvement after 24 weeks. Novikov et al. (2013) (29) reported that 89% of the patients treated with anti TNF therapy in Takayasu's arteriitis resulted in an improvement of clinical and laboratory signs. In this study ADA was well tolerated and similar results were found by Perra et al. (28) as well as Novikov et al. (29). Furthermore no side effects were observed in all studies. Even after a long term anti TNF therapy, the risk of an infectious complication was low (29).

In this study after six and 24 weeks of treatment with TCZ, the daily GCs dosage was reduced. The CRP level decreased after six, but increased slightly after 24 weeks compared to week six. The leucocytes count was elevated in the beginning of the study but then decreased to the physiological range. The reason

for this decrease was most likely due to the facts that – on the one hand – the daily GCs dosage had been reduced and – on the other hand – the inflammation was controlled by the biological agents. Two patients with temporal arteriitis were treated with TCZ. They both had a clinical improvement after 24 weeks. Loricera et al. (2015) (30) reported that 19 of 22 patients with temporal arteriitis treated with TCZ achieved a clinical improvement (86%). A patient with Takayasu's arteriitis was treated with TCZ. The patient achieved a clinical improvement after six weeks, however no improvement after 24 weeks. Osman et al. (2015) (31) reported in their case series that all three patients with Takayasu's arteriitis treated with TCZ markedly improved at the three months follow up. One patient with Castleman's disease was treated with TCZ. Six and 24 weeks after treatment begin, a clinical improvement was observed. Nagao et al. (2014) (32) published two case reports of patients with Castleman's disease. They were both treated with TCZ and became symptom-free after 8 to 10 weeks. However, 15 to 22 weeks after treatment start, they both had a relapse and the TCZ therapy was discontinued. They both received RTX and no further relapse was reported. Otherwise, Kawabata et al. (2013) (33) presented the case of a patient with Castleman's disease, who was successfully treated with TCZ.

Four patients with juvenile idiopathic arthritis were treated with ANK. Three of the four patients displayed a clinical improvement after six and 24 weeks. The other patient achieved no clinical improvement. Pardeo et al. (2015) (34) reported that after six months of treatment with ANK 14 of 25 (56%) patients (median age 5.8 years) with JIA met the criteria for inactive disease. Two patients with PFAPA syndrome were treated with ANK. One had a clinical improvement after six and 24 weeks, the other did not improve after six weeks and was then lost to follow up. A recent study suggests that treatment with ANK reduces the duration of an acute flare (35). One patient with TRAPS was treated with CKN and showed an improvement after 24 weeks of treatment. La Torre et al. (2015) (36) authored a case report of a patient with TRAPS treated with CKN. After the three and nine month follow-up, the TRAPS disease manifestations were still controlled.

The strength of this study is that it describes a collective of patients suffering from inflammatory diseases with respect to their response to biological treatment. This novel therapeutic options seem to be promising. However, data about its efficacy and safety are still rather rare in the here studied indications. This systematic analysis clearly demonstrated the usefulness of these molecules in the treatment of inflammatory diseases. Therefore, this study adds importantly to establishing novel treatment options in daily clinical practice and contributes to a better knowledge about a successful, safe and novel therapy for the treatment of inflammatory diseases.

The limitation of this study is that it is a retrospective, single center study based on the analysis of medical files meaning that the data were not collected in a standardized manner and the biological agents were only given to patients with severe or relapsing inflammatory diseases. Additionally, the effect of the biologicals was not controlled appropriately with the effect of GCs and other immunosuppressive agents such as CYC or MTX, in that particular patient collective. Moreover, it has to be taken into account that the sample size is low.

In summary, it can be stated that in this study patients with severe or relapsing inflammatory diseases were treated with biologicals. The laboratory inflammation parameters, the GCs dosage as well as other laboratory parameters were measured within a time period of six months after the first biological administration. Despite the above mentioned limitations of this study, we it shows that the GCs dosage can be reduced and the laboratory inflammation parameters tend to normalization. Therefore, biologicals should always be considered if a patient with severe or relapsing inflammatory diseases cannot be treated with the standard immunosuppressive therapy. However, further studies are required in order to define the possibilities and limitations of this indication for the use of biologicals in inflammatory diseases treatment more precisely.

References

1. Basu N, Watts R, Bajema I, et al. EULAR points to consider in the development of classification and diagnostic criteria in systemic vasculitis. Ann Rheum Dis. 2010;69:1744-1750
2. Reinhold-Keller E, Herlyn K, Wagner-Bastmeyer R, et al. Stable incidence of primary systemic vasculitides over five years: results from the German vasculitis register. Arthritis Rheum. 2005;53:93-99
3. Silva-Fernández L, Loza E, Martínez-Taboada VM, et al. Biological therapy for systemic vasculitis: a systematic review. Semin Arthritis Rheum. 2014;43:542-557
4. Waller R, Ahmed A, Patel I, et al. Update on the classification of vasculitis. Best Pract Res Clin Rheumatol. 2013;27:3-17
5. Luqmani RA, Pathare S, Kwok-Fai TL. How to diagnose and treat secondary forms of vasculitis. Best Pract Res Clin Rheumatol. 2005;19:321-336
6. D'Cruz DP, Khamashta MA, Hughes GR. Systemic lupus erythematosus. Lancet. 2007;369:587-596
7. Choi J, Kim ST, Craft J. The pathogenesis of systemic lupus erythematosus-an update. Curr Opin Immunol. 2012;24:651-657
8. Hui-Yuen JS, Li XQ, Askanase AD. Belimumab in systemic lupus erythematosus: a perspective review. Ther Adv Musculoskelet Dis. 2015;7:115-121
9. Hoffman GS, Kerr GS, Leavitt RY, et al. Wegener granulomatosis: an analysis of 158 patients. Ann Intern Med. 1992;116:488-498
10. Gayraud M, Guillevin L, le Toumelin P, et al. Long-term followup of polyarteritis nodosa, microscopic polyangiitis, and Churg-Strauss syndrome: analysis of four prospective trials including 278 patients. Arthritis Rheum. 2001;44:666-675
11. Reinhold-Keller E, Beuge N, Latza U, et al. An interdisciplinary approach to the care of patients with Wegener's granulomatosis: long-term outcome in 155 patients. Arthritis Rheum. 2000;43:1021-1032
12. Huscher D, Thiele K, Gromnica-Ihle E, et al. Dose-related patterns of glucocorticoid-induced side effects. Ann Rheum Dis. 2009;68:1119-1124
13. Wei L, MacDonald TM, Walker BR. Taking glucocorticoids by prescription is associated with subsequent cardiovascular disease. Ann Intern Med. 2004;141:764-770
14. Messer J, Reitman D, Sacks HS, et al. Association of adrenocorticosteroid therapy and peptic-ulcer disease. N Engl J Med. 1983;309:21-24
15. Piper JM, Ray WA, Daugherty JR, et al. Corticosteroid use and peptic ulcer disease: role of nonsteroidal anti-inflammatory drugs. Ann Intern Med. 1991;114:735-740
16. Bolanos SH, Khan DA, Hanczyc M, et al. Assessment of mood states in patients receiving long-term corticosteroid therapy and in controls with patient-

rated and clinician-rated scales. Ann Allergy Asthma Immunol. 2004;92:500-505

17. Skalka HW, Prchal JT. Effect of corticosteroids on cataract formation. Arch Ophthalmol. 1980;98:1773-1777
18. Johannesdottir SA, Horváth-Puhó E, Dekkers OM, et al. Use of glucocorticoids and risk of venous thromboembolism: a nationwide population-based case-control study. JAMA Intern Med. 2013;173:743-752
19. Canalis E, Mazziotti G, Giustina A, et al. Glucocorticoid-induced osteoporosis: pathophysiology and therapy. Osteoporos Int. 2007;18:1319-1328
20. Ritter A, Burow A, Vallelian F, et al. [Systemic glucocorticoids: diagnosis, prophylaxis and treatment of side effects]. Praxis (Bern 1994). 2014;103:987-998; quiz 996
21. Gómez-Puerta JA, Quintana LF, Stone JH, et al. B-cell depleting agents for ANCA vasculitides: a new therapeutic approach. Autoimmun Rev. 2012;11:646-652
22. Smith RM, Jones RB, Guerry MJ, et al. Rituximab for remission maintenance in relapsing antineutrophil cytoplasmic antibody-associated vasculitis. Arthritis Rheum. 2012;64:3760-3769
23. Guillevin L, Pagnoux C, Karras A, et al. Rituximab versus azathioprine for maintenance in ANCA-associated vasculitis. N Engl J Med. 2014;371:1771-1780
24. Cartin-Ceba R, Golbin JM, Keogh KA, et al. Rituximab for remission induction and maintenance in refractory granulomatosis with polyangiitis (Wegener's): ten-year experience at a single center. Arthritis Rheum. 2012;64:3770-3778
25. Díaz-Lagares C, Croca S, Sangle S, et al. Efficacy of rituximab in 164 patients with biopsy-proven lupus nephritis: pooled data from European cohorts. Autoimmun Rev. 2012;11:357-364
26. Dass S, Bowman SJ, Vital EM, et al. Reduction of fatigue in Sjögren syndrome with rituximab: results of a randomised, double-blind, placebo-controlled pilot study. Ann Rheum Dis. 2008;67:1541-1544
27. Devauchelle-Pensec V, Mariette X, Jousse-Joulin S, et al. Treatment of primary Sjögren syndrome with rituximab: a randomized trial. Ann Intern Med. 2014;160:233-242
28. Perra D, Alba MA, Callejas JL, et al. Adalimumab for the treatment of Behçet's disease: experience in 19 patients. Rheumatology (Oxford). 2012;51:1825-1831
29. Novikov PI, Smitienko IO, Moiseev SV. Tumor necrosis factor alpha inhibitors in patients with Takayasu's arteritis refractory to standard immunosuppressive treatment: cases series and review of the literature. Clin Rheumatol. 2013;32:1827-1832
30. Loricera J, Blanco R, Hernández JL, et al. Tocilizumab in giant cell arteritis: Multicenter open-label study of 22 patients. Semin Arthritis Rheum. 2015;44:717-723

31. Osman M, Emery D, Yacyshyn E. Tocilizumab for Treating Takayasu's Arteritis and Associated Stroke: A Case Series and Updated Review of the Literature. J Stroke Cerebrovasc Dis. 2015;24:1291-1298
32. Nagao A, Nakazawa S, Hanabusa H. Short-term efficacy of the IL6 receptor antibody tocilizumab in patients with HIV-associated multicentric Castleman disease: report of two cases. J Hematol Oncol. 2014;7:10
33. Kawabata H, Kotani S, Matsumura Y, et al. Successful treatment of a patient with multicentric Castleman's disease who presented with thrombocytopenia, ascites, renal failure and myelofibrosis using tocilizumab, an anti-interleukin-6 receptor antibody. Intern Med. 2013;52:1503-1507
34. Pardeo M, Pires Marafon D, Insalaco A, et al. Anakinra in Systemic Juvenile Idiopathic Arthritis: A Single-center Experience. J Rheumatol. 2015;42:1523-1527
35. Stojanov S, Lapidus S, Chitkara P, et al. Periodic fever, aphthous stomatitis, pharyngitis, and adenitis (PFAPA) is a disorder of innate immunity and Th1 activation responsive to IL-1 blockade. Proc Natl Acad Sci U S A. 2011;108:7148-7153
36. La Torre F, Muratore M, Vitale A, et al. Canakinumab efficacy and long-term tocilizumab administration in tumor necrosis factor receptor-associated periodic syndrome (TRAPS). Rheumatol Int. 2015;35:1943-1947

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Appendix

Table 1: Patient characteristics anti CD20 antibody (rituximab, n = 18)

	number	diagnosis	sex	age	clinical improvement		pretreatment	concurrent medication		
					6 w	24 w		start	6 w	24 w
RTX	1	granulomatosis with polyangiitis	m	44	y	y	cyclophosphamide, prednisone, azathioprine, MTX	prednisone 30mg/d, mycophenolic acid 1,5g/d, cyclophosphamide 1.2g every 3 week	prednisone 30mg/d, mycophenolic acid 2g/d	prednisone 7.5mg/d, mycophenolic acid 800mg/d
	2	granulomatosis with polyangiitis	f	50	no data	y	cyclophosphamide, methylprednisolone, prednisone, azathioprine, MTX	prednisone 65mg/d	no data	prednisone 7.5mg/d, MTX 20mg/w
	3	granulomatosis with polyangiitis	m	54	no data	y	MTX, prednisone	prednisone 60mg/d	prednisone 20mg/d, azathioprine 150 mg/d	prednisone 15mg/d, azathioprine 150mg/d
	4	granulomatosis with polyangiitis	m	33	y	y	azathioprine, cyclophosphamide, MTX, mycophenolic acid, prednisone	prednisone 20mg/d, mycophenolic acid 2g/d	prednisone 20mg/d, mycophenolic acid 2g/d	prednisone 5mg/d, mycophenolic acid 2g/d
	5	granulomatosis with polyangiitis	m	38	y	y	prednisone, MTX, azathioprine	azathioprine 200mg/d	azathioprine 200mg/d	azathioprine 200mg/d
	6	granulomatosis with polyangiitis	m	62	y	y	prednisone, azathioprine, mycophenolic acid, MTX	prednisone 20mg/d, MTX 10mg/w	prednisone 15mg/d, MTX 20mg/w	prednisone 10mg/d, MTX 20mg/w
	7	granulomatosis with polyangiitis	f	60	y	y	prednisone	prednisone 40mg/d	prednisone 7.5mg/d	prednisone 5mg/d
	8	systemic lupus erythematosus	f	31	y	y	none	prednisone 40mg/d, mycophenolic acid 1.5g/d, hydroxychloroquine 400mg/d	prednisone 7.5mg/d, mycophenolic acid 3g/d, hydroxychloroquine 400mg/d	prednisone 5mg/d, mycophenolic acid 3g/d, hydroxychloroquine 400mg/d

	9	systemic lupus erythematosus	f	53	n	n	prednisone, cyclophosphamide, mycophenolic acid, azathioprine, hydroxychloroquine	prednisone 20mg/d, azathioprine 150mg/d	prednisone 10mg/d, azathioprine 150mg/d	prednisone 5mg/d, azathioprine 150mg/d
	10	systemic lupus erythematosus	f	33	n	n	prednisone, hydroxychloroquine, cyclophosphamide, azathioprine	prednisone 40mg/d, azathioprine 100mg/d, hydroxychloroquine 200mg/d	prednisone 80mg/d, azathioprine 100mg/d, hydroxychloroquine 200mg/d	prednisone 20mg/d, azathioprine 100mg/d, hydroxychloroquine 200mg/d, imatinib 200mg/d
	11	systemic lupus erythematosus	f	36	y	y	prednisone, hydroxychloroquine	prednisone 10mg/d, mycophenolic acid 2g/d	prednisone 10mg/d, mycophenolic acid 2g/d	prednisone 8mg/d, mycophenolic acid 2g/d
	12	Sjögren's syndrome	f	52	y	no data	prednisone, azathioprine	prednisone 2.5mg/d, azathioprine 100mg/d	prednisone 2.5mg/d, azathioprine 100mg/d	azathioprine 100mg/d, hydroxychloroquine 400mg/d
	13	Sjögren's syndrome	m	64	n	y	prednisone, cyclophosphamide	prednisone 30mg/d	prednisone 30mg/d	prednisone 7.5mg/d, azathioprine 100mg/d
	14	Sjögren's syndrome	f	71	no data	y	prednisone, cyclophosphamide, azathioprine	prednisone 15mg/d	no data	prednisone 7.5mg/d
	15	microscopic polyangiitis	f	69	y	y	prednisone, azathioprine, cyclophosphamide, mycophenolic acid	prednisone 60mg/d, mycophenolic acid 150mg/d	prednisone 50mg/d, mycophenolic acid 1g/d	prednisone 7.5mg/d, mycophenolic acid 1g/d
	16	myasthenia gravis	f	53	no data	y	prednisone, azathioprine, mycophenolic acid	mycophenolic acid 2g/d	no data	mycophenolic acid 1g/d
	17	suspected ORL manifestation of an IgG4 related disease	f	55	y	y	prednisone	prednisone 10mg/d	prednisone 7.5mg/d	prednisone 5mg/d
	18	eosinophilic granulomatosis with polyangiitis	f	44	y	y	prednisone, cyclophosphamide	prednisone 65mg/d	prednisone 40mg/d	prednisone 7.5mg/d

Table 2: Patient characteristics anti TNF antibodies (adalimumab, infliximab, etanercept), n = 10

	number	diagnosis	sex	age	clinical improvement		pretreatment	concurrent medication		
					6 w	24 w		start	6 w	24 w
ADA	1	Behcet's disease	m	43	y	n	prednisone, azathioprine, mycophenolic acid, cyclophosphamide	prednisone 40mg/d, mycophenolic acid 1g/d	prednisone 15mg/d, mycophenolic acid 2g/d	prednisone 20mg/d, mycophenolic acid 1g/d
	2	Behcet's disease	m	31	y	y	prednisone, azathioprine, colchicine	prednisone 20mg/d, azathioprine 150mg/d	prednisone 10mg/d	prednisone 7.5mg/d, colchicine 1mg/d
	3	Takayasu's arteriitis	f	37	no data	y	prednisone, IFX, MTX	prednisone 7.5mg/d, MTX 7.5mg/w	prednisone 7.5mg/d	prednisone 7.5mg/d
	4	Takayasu's arteriitis	f	31	n	y	prednisone, azathioprine	prednisone 30mg/d, azathioprine 100mg/d	prednisone 10mg/d, azathioprine 100mg/d	prednisone 10mg/d, azathioprine 100mg/d
	5	undifferentiated small vessel vasculitis	f	39	n	y	azathioprine, prednisone, methylprednisolone, cyclophosphamide, mycophenolic acid	prednisone 40mg/d	prednisone 50mg/d	prednisone 7.5mg/d
	6	Henoch–Schoenlein purpura	f	75	n	y	prednisone	prednisone 10mg/d	prednisone 5mg/d	none
	7	polyarteriitis nodosa	f	33	y	y	prednisone, mycophenolic acid, azathioprine, MTX, methylprednisolone, cyclophosphamide	prednisone 100mg/d, mycophenolic acid 1g/d	prednisone 40mg/d, mycophenolic acid 1g/d	prednisone 17.5mg/d, mycophenolic acid 1g/d
	8	ulcerative leukocytoclastic vasculitis	f	48	n	y	prednisone, mycophenolic acid, azathioprine, thalidomide, melphalan, cyclophosphamide	prednisone 40mg/d, mycophenolic acid 1.5g/d	prednisone 50mg/d, mycophenolic acid 1.5g/d	prednisone 7.5mg/d, mycophenolic acid 1g/d
IFX	9	recurrent polychondritis	m	75	n	-	prednisone, azathioprine, MTX	prednisone 20mg/d	prednisone 20mg/d	patient died

ETN	10	tumor necrosis factor receptor-associated periodic syndrome (TRAPS)	m	35	no data	no data	prednisone	prednisone 60mg/d	no data	no data

Table 3: Patient characteristics anti interleukin agents (tocilizumab, anakinra, canakinumab), n = 16

	number	diagnosis	sex	age	clinical improvement		pretreatment	concurrent medication		
					6 w	24 w		start	6 w	24 w
TCZ	1	temporal arteriitis	m	69	y	y	prednisone, MTX	prednisone 12.5mg/d, MTX 10mg/w	prednisone 7.5mg/d	prednisone 4.5mg/d
	2	temporal arteriitis	f	75	n	y	prednisone, MTX	prednisone 7.5mg/d MTX 15mg/w	prednisone 10mg/d	prednisone 15mg/d, MTX 15mg/w
	3	large vessel vasculitis	f	64	y	y	prednisone, MTX	prednisone 17.5mg/d, MTX 20mg/w	prednisone 5mg/d, MTX 20mg/w	prednisone 5mg/d, MTX 20mg/w
	4	Takayasu's arteriitis	f	40	y	n	prednisone, MTX, ADA, IFX	prednisone 10mg/d	prednisone 5mg/d	none
	5	Castleman's disease	f	43	y	y	prednisone	prednisone 10mg/d	prednisone 10mg/d	none
ANK	6	juvenile idiopathic arthritis	f	32	n	n	prednisone	prednisone 50mg/d	prednisone 10mg/d	prednisone 20mg/d
	7	juvenile idiopathic arthritis	f	36	y	y	prednisone, MTX, azathioprine	prednisone 7.5mg/d	prednisone 5mg/d	prednisone 3.5mg/d
	8	juvenile idiopathic arthritis	f	32	y	y	prednisone, ETN, azathioprine	prednisone 50mg/d	prednisone 7.5mg/d	none
	9	juvenile idiopathic arthritis	f	27	y	y	prednisone, cyclosporin	dexamethasone 8mg/d	cyclosporin 100mg/d	cyclosporin 50mg/d
	10	PFAPA syndrome	f	23	y	y	prednisone	none	none	none
	11	PFAPA syndrome	f	22	n	no data	none	none	none	none
	12	Behcet's disease	f	29	n	y	prednisone, colchicine, azathioprine, golimumab	none	none	none
	13	chronic systemic inflammation	f	63	n	y	prednisone, azathioprine	prednisone 15mg/d	prednisone 10mg/d	prednisone 7.5mg/d
	14	neutrophilic dermatosis	f	62	y	y	prednisone, colchicine, hydroxychloroquine, dapsone, cyclosporin	prednisone 20mg/d	none	none
	15	chronic systemic inflammation	f	55	n	no data	prednisone	prednisone 20mg/d, colchicine 1mg/d	prednisone 7.5mg/d	no data

CKN	16	tumor necrosis factor receptor-associated periodic syndrome (TRAPS)	m	35	no data	y	ETN	prednisone 20mg/d	no data	no data

Curriculum Vitae

Name, Given Name	Manz, Salomon Miro
Date of Birth:	April 19, 1991
Place of Origin:	Rafz ZH

Education

1997 – 2003	Primary School Hasenbuhl in Uster
2003 – 2005	Academic High School (in German: Kantonsschule) Hohe Promenade in Zurich
2005 – 2009	Academic High School (in German: Kantonsschule) Hottingen in Zurich
	Matura in Business and Law
2010 – 2013	University of Zurich, Bachelor of Medicine UZH (B Med)
2013 – 2016	University of Zurich, Master of Medicine UZH (M Med)

Employment

Since 2017	Assistant doctor, Uster General Hospital, Department of Internal Medicine